Neuronal activity after cocaine self-administration

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Drug addiction is a chronic, relapsing brain disorder characterized by compulsive drug seeking and taking in spite of negative consequences. It poses legal, economic and health problems that bear on both the individual users and the society as a whole. Understanding the brain mechanisms through which intake of the drug leads to substance use disorder will be important to find solutions for such diseases. In the current thesis we focus on the neurobiological mechanisms of cocaine addiction, more specifically on the functional alterations of several brain areas known to be involved in addiction, i.e., the prefrontal cortex (PFC), striatum, and lateral habenula. Using immediate early genes as neuronal reactivity markers, we analyzed changes in the neuronal activation in these brain regions after a short-term (10 days) and long-term (60 days) cocaine self-administration. In our first experiment, we observed that cocaine self-administration increased the expression of multiple IEGs in medial PFC, dorsal and ventral striatum in both 10 days and 60 days experiments. Among these IEGs, six of them (*c-fos*, *Mkp1*, *Fosb/ΔFosb*, *Egr2*, *Arc* and *Egr4)* were found to respond to cocaine self-administration in all three regions. Considering the possibilities of heterogeneous expression patterns of IEGs, we then measured the cellular expression level of *Mkp1* in specific subregions, but also analyzed the distribution patterns of the *Mkp1*-labeled neurons in the medial PFC, orbitofrontal cortex, and striatum. We showed that 10 days of cocaine self-administration produced strong neuronal reactivity in the dorsal part of the medial PFC, the medial and central parts of the orbitofrontal cortex, and the dorsomedial and ventrolateral striatum. In contrast, 60 days of cocaine exposure generated much less increases of neuronal reactivity in cortex, which were found mainly at the posterior level. In striatum the main reactions to cocaine were largely observed in the medial and central parts of the dorsal striatum. In the final experiment, we investigated the changes in neuronal activation in the medial (LHbM) and lateral (LHbL) subnuclei of the lateral habenula using the IEG *c-fos*. We found that 10 days of cocaine self-administration significantly increased the density and intensity of *c-fos* positive neurons in the LHbL. By contrast, 60 days of cocaine self-administration increased in the density of *c-fos* positive neurons in both LHbL and LHbM. In addition, we showed that cocaine self-administration increased the GABAergic neuronal activity in the rostromedial tegmental nucleus after 10 days, but not after 60 days, exposure. Taken together, we concluded that cocaine self-administration produced neuronal activation in the prefrontal-striatal circuits and subnuclei of the lateral habenula, which may indicate the rewarding and aversive effects of cocaine on the brain. Alterations in the neuronal activation also suggested the changes of brain function during the development of drug use, when the cocaine self-administration was extended from short-term to long-term. It revealed that cocaine self-administration affected the brain in a complexity and dynamic way in the development of drug addictive behavior.